DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

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National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

FAQ: Making PET tracers for NCI-DCTD Sponsored Trial

Audience: Study PI, Site Nuclear Medicine PI, Site PI, Site Radiochemist/Radiopharmacist

Basics

1. Why is NCI putting all of these extra requirements on our manufacturing process?
    a. NCI performs multicenter trials and it is essential that all drugs and procedures used in a multicenter trial are as much the same as possible, which includes imaging drugs and procedures. Since PET drugs must be made in a decentralized manner, assuring that they have identical quality is of the utmost importance.
    b. If the quality characteristics of a PET radiopharmaceutical is not controlled for when conducting a multicenter trial, this could lead to different sites making agents which are nominally the same but could have different properties due to differences in the quality control specifications. This would confound the interpretation of imaging findings and lessen the likelihood of useful imaging data. Such a situation must be avoided as it can lead to research that is both unethical and devoid of scientific value.
2. What do I need to do to make tracers at my site for an NCI-sponsored clinical trial?
    a. You must have the appropriate facility and resources to make investigational PET agents: cyclotron or acceptable supply of F-18 to use, radiochemist, radiopharmacist, etc.
    b. You must have evidence of experience in manufacturing PET drugs for clinical trials or clinical care, documented by experience with manufacturing approved agents (like FDG) under NDA/ANDA or investigational agents under IND.
    c. You must have a Type II Drug Master File (DMF) or Investigational New Drug Exemption (IND) *active* at the FDA for the agent – but see below regarding your site's IND. Making the agent under RDRC is not acceptable for use in an NCI-DCTD sponsored trial; you must have an IND or have filed a DMF with the FDA for the agent.
    d. You must make the drug to ***identical*** specifications as the NCI specifications, with the only allowed exceptions listed below.
    e. You must provide evidence of having manufactured at least three batches of the agent that meet specifications in the last 12 months.
    f. You must meet all of the requirements in the SOP attached.
3. What is acceptable evidence of experience in manufacturing PET drugs for clinical trials or clinical care?
    a. 3 active INDs for PET drugs (RDRC will not suffice)
    b. *OR* an approved NDA or ANDA for a PET drug
    c. No outstanding FDA inspection issues

4. Do I have to go through this process for every trial my site does with a PET radiopharmaceutical?
    a. No, only for each specific PET radiopharmaceutical.
    b. An approval to manufacture a specific PET radiopharmaceutical to use in NCI-DCTD sponsored trials is good for that PET radiopharmaceutical, no matter how many trials that PET radiopharmaceutical is used in.
    c. We will ask for yearly or biennial table of lots made with specifications and analytical data for ongoing or newly proposed trial.
    d. An approval for a specific PET radiopharmaceutical does not approve you to manufacture a different PET radiopharmaceutical.
5. Who decides if we can supply radiopharmaceutical for a trial?
    a. The Cancer Imaging Program, which has the INDs for the trial.
    b. CTEP approval is required for DCTD-sponsored trials but CTEP approval is *not* sufficient to permit investigational IND agents to be used in a trial.
    c. No other NCI entity except CIP can authorize approval to supply investigational IND radiopharmaceuticals to a trial under a CIP/NCI IND.
6. Can commercial entities supply these agents?
    a. Yes.
    b. They must also have a DMF, supply a letter of authorization, and meet the same specifications as filed in the NCI IND

Specifications

1. What specifications must I meet?
    a. The specifications that are established in the NCI/CIP IND.
    b. The specifications must be *identical* to those in the NCI/CIP IND. NOT similar. NOT just acceptable to FDA for other trials you are sponsoring. IDENTICAL.
2. What if my specifications are not *identical?*
    a. If the lack of identity is because you have more stringent specifications (pH 6.5-7.5 instead of 6-8 for example), that is acceptable but you must be explicit about it in the documents in the same place that the specifications and lot data are presented.
    b. If the lack of identity is due to a different manufacturing process, for example, if you do not use acetone in your process, *explain* why it is not needed to analyze for and it will be acceptable *as long as* you analyze for all other solvents in your process.
    c. If the lack of identity is due to a different expression of the value – you must add an explanation that fully reconciles the expressions. Examples: mass per dose vs. mass per ml, so we don't have to search for your maximum dose volume. Specific activity vs. mass dose and activity strength. As long as you *provide* the explanation in the *same* place as the specifications and the lot data are presented, that will be acceptable.
    d. If your specifications are not *identical* but your lot data indicates you can meet the NCI IND specifications, we will ask you to change your specifications in your DMF/IND while we provisionally approve you to make the agent.

e. If your specifications are not identical and your lot data indicates that you cannot reliably meet the specifications, we will reject your application until you provide evidence you can both meet the requirements and formally change your specifications.

3. Your specifications should be presented in a table alongside of the NCI specifications with appropriate comments and explanations. We will provide template tables for the PET radiopharmaceuticals that can be supplied under this process.

Batch records

1. Do I need to manufacture by the same procedure as NCI (method, precursor)?
    a. No.
    b. However, you must meet the ***identical*** specifications unless as noted above. If the lack of identity is due to a different manufacturing process, for example, if you do not use acetone in your process, ***explain*** why it is not needed to analyze for and it will be acceptable as long as you analyze for other solvents in your process.
2. What data must I provide to show compliance?
    a. At least three lots, preferably consecutive, that meet every specification including sterility, that have been prepared in the last 12 months.
    b. A table of all of the lots prepared in the last 12 months, passing or failing.
    c. Data for the three lots can be presented either a table of values vs. specifications or as QC approval sheets.
3. Do I need to include full batch record and/or QC analyses?
    a. No. If you decide to include an example, please put it as an appendix so we don't have to go through hundreds of pages to get to the lot data tables.
    b. We might request an example if there appears to be some issue, but it is unlikely.

Regulatory

1. What do I need to provide NCI for NCI's regulatory filing?
    a. You need to give us a letter of right of reference (a.k.a. cross-file letter, letter of authorization) to your active Type II DMF or IND for this agent. See the example.
    b. You need to file a copy of this letter to the FDA with your DMF or your IND, whichever you are using.
    c. We will file the same letter to the NCI IND.
2. Which IND is the official sponsor for this trial?
    a. NCI is the official sponsor and the trial is performed under the NCI IND even if you also have an IND.
    b. If you have an active IND for the same agent, you should NOT file this protocol to it, nor adverse events etc.
    c. NCI is the sponsor, files the protocol, reports adverse events, updates the investigator brochure, etc.
3. Should I file a DMF or an IND?

   a. Either is acceptable to provide a letter of right of reference to the CMC for the NCI IND to file that permits you to make radiopharmaceutical for this trial.
   b. If you have no active IND, file a DMF. Should you later wish to do a different trial with this agent, you can file that later IND with a reference letter to the DMF you will be submitting for the current trial.
   c. If you have an active IND for this agent that was established for other clinical trials, provide a letter that only permits reference to the CMC sections (See example)
   d. You may choose to file a new IND if there are other trials you would like to do, but do NOT use this protocol as the activating trial.
   e. [If you decide to file a new IND with another trial, NCI recommends that you request a reference letter to the NCI pharmacology & toxicology data in our IND, as that will make your filing easier, but you do not have to do this.]
4. This process seems very convoluted and circular, maybe even improper. Are you sure?
   a. Yes, we are sure.
   b. The process of right of reference allows any set of documentations from any regulatory filing to be incorporated by reference into any other. It does not matter who gives the letter or who takes it, just that what it authorizes is now legally in the new filing.
   c. The referred information is NOT repeated in the new filing, all that is needed is the letter. This process helps both sponsor and FDA to avoid re-review of already reviewed data

Supply of IND Agents to NCI-sponsored trials by Skilled Academic Sites

Paula M. Jacobs, Ph.D.
Associate Director, Division of Cancer Treatment and Diagnosis, NCI
Cancer Imaging Program

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Some Basic Issues

- Investigational drugs require an IND from the FDA to test in humans
- NCI requires that NCI "sponsor" the IND for our trials
  - Holds the IND, files new protocols to the NCI IND
  - Files annual reports
  - Files adverse event reports
- If you don't understand:
  - An Investigational New Drug (IND) file
  - A drug master file (Hint: the CMC section of an IND)
  - Letters of right of reference
  - This approach is not for you

Uses of DMF & IND

- DMF (Drug Master File)
  - Can manufacture for others with IND or NDA/ANDA by giving the other site a cross-file letter
  - Responsible for CMC only
- IND (Investigational New Drug Exemption)
  - Can perform clinical trials
  - If submit CMC, can manufacture for own trials
  - If give cross-file letter, can manufacture for IND trials sponsored by others

Letter of Right of Reference

- Also called: cross-file letter, letter of authorization (LOA)
- Incorporates the specified sections from one DMF, IND, or NDA into another by reference
- The information authorized is not repeated in the new IND and does not have to be provided to the new applicant
- All the new applicant needs is the letter

The holder of the original IND has no responsibility for the new IND

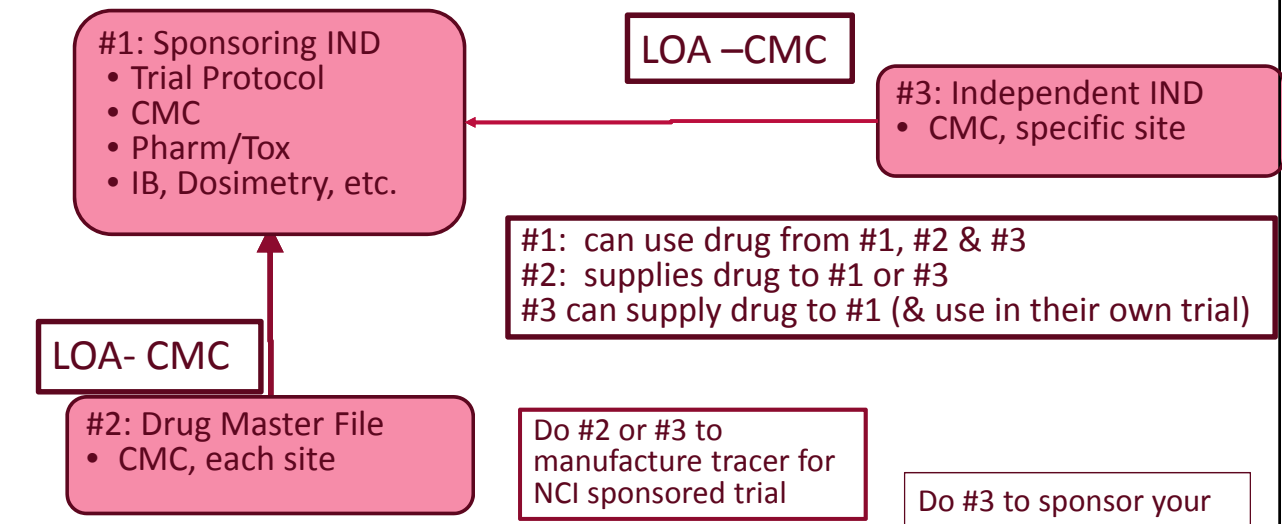
What does this accomplish?

- Whatever the letter references is legally incorporated in the IND to which it is given without actually copying it into the new IND
- Allows any entity (commercial or non-commercial) to supply drug for any IND with their site specific DMF or IND and an LOA
- Helps independent PIs to get their own IND – no need to repeat toxicity studies, for example
- Reduces FDA review time/effort

How Does This Work?

Interlocking regulatory documents

Flow chart



ECOG-ACRIN Example

- NCI IND for FMISO
  - One MF site filed in the IND – U Wash
  - One commercial entity with DMF filed
  - Mixture of academic and commercial acceptable
- Academic manufacturing sites possible
  - Process established to permit experienced academic radiochemistry/pharmacy sites to supply their own site

Requirements for Multiple Supply Sites

- The CMC for every site for the specific agent must be filed with FDA (DMF or IND)
- The agent must be "equivalent" across sites
- The agent must meet the NCI specifications
- The site must comply with USP<823> or 21CFR212
- The site must be experienced
- NCI is not responsible for site CMC compliance/filings

How can we assure this?

Approach

- Site must have active IND or DMF for the specific drug and supply an LOA to NCI
- IND or DMF must not be on hold
- The drug must meet NCI specifications
- Site experience is assured by:
  - Current NDA or ANDA for approved agent
  - **OR**–multiple active or recent INDs
  - Inspection records, no warning letters
  - Drug made in inspected facility

Approach (2)

- NCI holds the IND for the trial
  - Makes the regulatory filings for IND and trial
  - Monitors and reports Adverse events
  - Files the IND annual report
- Each manufacturing site:
  - Supplies its site with drug under GMP or USP<823>
  - Maintains its DMF or IND current
  - Notifies entities as required (FDA, NCI, other sites supplied) of MF deviations/failures, etc.

What goes in a DMF (or the CMC section of IND)

Chemistry Manufacturing and Controls (CMC) for each and every site that manufactures

- Detailed manufacturing information
- Detailed packaging & labeling information
- Detailed quality control procedures
- Release specifications
- Facility information
- Results from at least 3 batches
- Stability data

Appendix 1:

Regulatory approach to approve manufacturing sites to make IND PET agents to be used under a Cancer Imaging Program (CIP) IND for a specified trial

Principles:

1. The trial PI is responsible for collecting all of the documentation required from each study site and submitting it, as a complete package, through CTEP PIO.
2. A pre-qualification check-list that will limit this approach to highly experienced manufacturing sites will be developed for each trial by a cooperative group, a consortium or an individual PI, and approved by CIP/NCI (CIPindagents@mail.nih.gov).
3. Only study sites that have filed ANDAs or NDAs for clinical PET drugs and/or have active INDs for 3 or more PET radiopharmaceutical drugs can be considered. Copies of recent FDA inspection reports and other regulatory documentation will be required.
4. The study site must have a DMF or IND with complete CMC for the specific investigational drug, filed and active with the FDA.
5. The study site FDA filing must be kept current and compliant, and not be on hold.
6. The study site must certify that they meet the same specifications as in the CIP/NCI IND and provide current analytical/QC data from recently manufactured lots.
7. The study site may have more stringent specifications but not less than the CIP/NCI IND.
8. This process is under the responsibility of the Cancer Imaging Program. No other NCI entity can authorize approval to supply investigational IND radiopharmaceuticals to a trial under a CIP/NCI IND. CTEP approval is required for DCTD-sponsored trials but CTEP approval is not sufficient to permit investigational IND agents to be used in a trial.
9. The process, as for commercial suppliers, must be in accordance with FDA current regulations for PET agents. (See list of FDA regulations and guidances at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm)

Mechanism:

1. The trial PI provides CIP/NCI through the CTEP PIO with the documentation listed in the attached check list.
2. CIP/NCI verifies that the site's manufacturing specifications are in accordance with the CIP/NCI specifications.
3. Each study site, through the trial PI and CTEP PIO, provides CIP/NCI with a letter of right of reference to the CMC information in their filing, which CIP/NCI files to the CIP/NCI open IND and each study site files to their open DMF or IND.
4. Pre-qualification check list for each agent is developed by the group or PI with CIP regulatory concurrence.
5. The individual study site documentation should be processed by the PI, group or consortium but the final decision is with CIP/NCI regulatory.

Responsibilities:

1. CIP/NCI: Sponsor of record for trial (IND Protocol Sponsor)
    a. Regulatory filings for the CIP/NCI IND and the specific clinical trial

b. Adverse event monitoring

c. Trial management and reporting

d. CIP/NCI is not responsible for the drug manufacture or any CMC filings (Letter of Authorization to Cross-Reference site's DMF or IND is filed with the CIP/NCI IND.)

2. Manufacturing site: Not a trial sponsor under the IND

a. Preparation and Product Accountability of the PET agent under either GMP or USP<823> (See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm.)

b. Maintaining the referenced DMF or IND filing current throughout lifecycle

c. Notification of manufacturing deviations, failures, supply issues for PET drug for the specified trial to appropriate regulatory bodies, and CIP/NCI, in accordance with applicable regulations and guidance

d. Site is not responsible for regulatory filings for the clinical trial

Checklist for Approval of Manufacturing Site Not Previously Approved by NCI CIP to Manufacture a Specific PET agent.

This Checklist can be used to submit updates or corrections.

Documents to be submitted by the trial PI through CTEP PIO to the CIP/NCI	Included	Comment
1. Site has successfully filed PET NDA or ANDA for clinical use or has ≥ 3 active PET INDs (not RDRC). Cover sheet for the most recent Annual Reports submitted for each one. If none yet, FDA acknowledgement letter provided to CIP.	□ Yes □ No	
2. Site has submitted latest FDA inspection report (Establishment Inspection Reports (EIR) and/or Form FDA-483) for their INDs, NDA or ANDA to CIP if any have been conducted.	□ Yes □ No	
3. Site has an active DMF or IND for this PET agent. Copy of last Annual Report submitted to CIP. If none yet, FDA acknowledgement letter provided to CIP.	□ Yes □ No	
4. Site can meet the same specifications in the NCI IND including expiration dating. Specification Sheet submitted to CIP with a comparison of the specifications	□ Yes □ No	
5. Site makes consistent product. Analytical Test Results submitted for last 12 months batch analyses, passed or failed. At least three lots must pass and no more than 10% fail for other than equipment failure.	□ Yes □ No	
6. Site commits to PET manufacturing stipulations (NCTN Group/Consortium/ ETCTN Study PI/CIP Pre-qualification Steps) for lifecycle of IND trial(s). Statement of Commitment on official letterhead provided to CIP.	□ Yes □ No	
7. Site provides CIP through trial PI with Letter of Authorization to Cross Reference to Site's DMF or IND, in order to include reference to this new/additional manufacturing information in CIP's IND. Site files letter with their application. CIP files letter with their IND for the Clinical Trial.	□ Yes □ No	
8. NCTN group/Consortium/ETCTN Study PI notifies CIP that they are satisfied with Site's manufacturing qualifications and commitment to compliance responsibilities and submits all of this documentation through CTEP PIO. *(**Stipulation list to be created by Group/CIP* See Points to Consider, on following page.**)*	□ Yes □ No	
9. CIP notifies site that the site is approved to supply PET agent for IND clinical trial.	□ Yes □ No	

*Key Points of Reference for Stipulation List:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM266640.pdf
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm
http://www.gpo.gov/fdsys/granule/CFR-2010-title21-vol4/CFR-2010-title21-vol4-part212/content-detail.html
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM277416.pdf
http://www.gpo.gov/fdsys/pkg/CFR-2010-title21-vol4/pdf/CFR-2010-title21-vol4-part212.pdf

Some Things to Consider for Pre-Qualification of Site (i.e., Generating Stipulation List)

- CMC may be in accordance with cGMP for PET (21CFR212), or USP<823>32nd Edition as permitted by 21CFR212.5(b)
- Provide Analytical Test Results for the last 12 months, both passing and failing batches
- Provide Certificate of Analysis with every lot
- Agreement that Academic Center has responsibility to inform all appropriate regulatory bodies and partners, including CIP and NCTN Group/Consortium/ETCTN partners, when conditions change; this includes, but is not be limited to the following situations: manufacturing deviations, failures, and supply issues, etc., in accordance with applicable regulations and policies.

Other requirements as appropriate for each trial

Appendix 2: Letter of authorization

Put your letterhead here

[Date]

Liberio Marzella, MD
Director, Division of Medical Imaging and Hematology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND Reference Letter of [site name] DMF or IND [#####]

Dear Dr. Marzella:

This letter is to authorize reference to [IND or DMF # xxxxxxx] for the manufacturing of [name the tracer]. Specifically we are allowing the individual or entity named below to reference the Chemistry, Manufacturing and Control information in the [IND or DMF]

Permission to reference [IND or DMF # xxxxxxx] is granted to:

Paula M. Jacobs, Ph.D.,
National Institutes of Health/NCI/DCTD
Associate Director DCTD, Cancer Imaging Program
9609 Medical Center Dr Rm 4W236, MSC 9729
Bethesda, MD 20892-9729
[FedEx: Rockville, MD 20852-4910]
Tel: 240-276-6510
jacobsp@mail.nih.gov

If you have any questions or require additional information, please do not hesitate to contact me.

Sincerely Yours,
[Insert here the name, title, full address and contact information for the individual responsible for the DMF or IND]

Appendix 3: Specification Sheets

Product Specifications for [F-18]FES

TEST	SPECIFICATION	Proposed site specifications	Comments
Chemical Purity (particulates)	Clear and Colorless		
pH	6 – 8		
Residual Kryptofix® [2.2.2]	< 50 µg/mL Kryptofix®		
Radiochemical Purity (HPLC)	> 95%		
Chemical Purity (HPLC)	FES < 5 µg per injected dose, other UV absorbing impurities beyond HPLC void volume (280 nm) ≤ 5 µg per injected dose		
Radiochemical Purity (TLC)	Rf > 0.5 Purity ≥ 95%		
Radionuclidic Purity	Measured half-life 100 – 120 minutes		
Residual Solvent Levels	Acetone < 5,000 ppm Acetonitrile < 400 ppm		
Bacterial Endotoxin	< 175 EU per dose		
Sterility	No growth observed in 14 days, also must pass filter integrity test		
Stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial with an expiration time of 8 hours			

Product Specifications for [F-18]FLT

Test	Specification	Proposed site specifications	Comments
Radiochemical Purity (TLC):	Rf = 0.4 – 0.7 Purity ≥ 95%		
Residual Solvent Levels:	Acetone < 5000 ppm Acetonitrile < 400 ppm DMSO < 5000 ppm		
Radionuclidic Purity:	Measured half-life 100 – 120 minutes		
Bacterial Endotoxin Levels:	< 175 EU per dose		
pH:	6 – 8		
Sterility:	no growth observed in 14 days		
Residual Kryptofix® [2.2.2]:	< 50 µg/ mL Kryptofix®		
Radiochemical Purity (HPLC):	> 95%		
Chemical Purity (HPLC):	FLT < 0.61 µg/ml Other < 1.2 µg/ml		
Chemical Purity (particulates):	Clear and Colorless		
Stored at room temperature in a septum sealed, sterile, pyrogen-free glass vial with an expiration time of 8 hours			

Product Specifications for [F-18]FMISO

Test	Specification	Proposed site specifications	Comments
Chemical Purity (particulates)	Clear, Colorless, No particulates		
pH	6-8		
Residual Kryptofix® [2.2.2]	< 50 µg/ mL Kryptofix®		
Radiochemical Purity (HPLC)	> 95%		
Chemical Purity (HPLC) **[by UV @327 (pref), 280, or 254 nm]**	FMISO < 15 µg per injected dose other < 35 µg / dose Specific impurities:~ 4.0min ≤ 3 µg/mL ~6.0 min ≤ 4 µg/mL		
Radiochemical Purity (TLC)	R_f = >0.5 Purity ≥ 95%		
Residual Solvent Levels	Acetone < 5000 ppm Acetonitrile < 400 ppm		
Radionuclidic Purity	Measured half-life 100-120 minutes		
Bacterial Endotoxin Levels	< 175 EU per dose		
Sterility	Negative/no growth, must also pass filter integrity test		
Stored iat room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial with an expiration time of 12 hours			